Peripersonal and extrapersonal visuospatial neglect in different frames of reference: A brain lesion-symptom mapping study

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Abstract

Introduction: Visuospatial neglect can occur in peripersonal and extrapersonal space. The dorsal visual pathway is hypothesized to be associated with peripersonal, and the ventral pathway with extrapersonal neglect. We aimed to evaluate neural substrates of peripersonal versus extrapersonal neglect, separately for egocentric and allocentric frames of reference.

Methods: This was a retrospective study, including stroke patients admitted for inpatient rehabilitation. Approximately 1 month post-stroke onset, computerized cancellation (egocentric) and bisection tasks (egocentric and allocentric) were administered at 30cm and 120cm. We collected CT or MRI scans and performed voxel-based lesion-symptom mapping for the cancellation, and subtraction analyses for the line bisection task.

Results: We included 98 patients for the cancellation and 129 for the bisection analyses. The right parahippocampal gyrus, hippocampus, and thalamus were associated with egocentric peripersonal neglect as measured with cancellation. These areas were also associated with extrapersonal neglect, together with the right superior parietal lobule, angular gyrus, supramarginal gyrus, lateral occipital cortex, planum temporale and superior temporal gyrus. Lesions in the right parietal, temporal and frontal areas were associated with both peripersonal and extrapersonal egocentric neglect as measured with bisection. For allocentric neglect no clear pattern of associated brain regions was observed.

Discussion: We found right hemispheric anatomical correlates for peripersonal and extrapersonal neglect. However, no brain areas were uniquely associated with peripersonal neglect, meaning we could not conclusively verify the ventral/dorsal hypothesis. Several areas were uniquely associated with egocentric extrapersonal neglect, suggesting that these brain areas can be specifically involved in extrapersonal, but not in peripersonal, attention processes.

Keywords: stroke, hemispatial neglect, peripersonal, extrapersonal, cancellation, lesion-symptom mapping

Abbreviations: CoC, centre of cancellation; FDR, false discovery rate threshold; MMSE, Mini-Mental State Examination; MNI, Montreal Neurological Institute; ROI, region of interest; SAN, Stichting Afasie Nederland; VLSM, voxel-based lesion-symptom mapping.

1. Introduction

Visuospatial neglect ('neglect') is a disabling disorder that is frequently observed after a stroke. It is a complex multi-component disorder [1,2], and can occur in most, if not all, sensory modalities as well as in the motor domain [3–5]. Patients with neglect have a deficit in lateralised attention [6]. They show no, or less, explorative behaviours and actions directed towards stimuli (usually) on the contralesional side. The lateralised attention deficit is more common and more severe after a stroke in the right hemisphere [7–9]. Negative consequences in daily life activities, however, are largely comparable between left and right-sided neglect [9]. Neglect can manifest in peripersonal space (i.e., within reaching distance; near) or extrapersonal space (i.e., beyond reaching distance; far) [10–13]. Traditional paper-and-pencil testing methods can, almost by definition, only assess neglect in peripersonal space. Alternative, experimental measures to assess extrapersonal neglect exist. Classic neglect tasks, such as line bisection [12,14] or cancellation [11], can be presented beyond reaching distance. Double dissociations and differences regarding neglect severity exist between peripersonal and extrapersonal neglect [10–12,14–16]. In addition, peripersonal and extrapersonal neglect differ regarding consequences on activities of daily living [17–19]. For example, explorative studies showed that only patients with peripersonal neglect have balance problems and problems in several daily life activities, such as finding personal belongings, whereas patients with extrapersonal neglect mainly showed problems with way finding [17,18].

The aim of the current study was to identify brain lesion locations associated with neglect in peripersonal and extrapersonal space. Previc [20] was one of the first to argue that processing visuo-spatial information in different regions of space relies on different neural mechanisms. The dorsal visual pathway (i.e., the inferior parietal cortex) would be more important in the processing of visuo-spatial information in peripersonal space, whereas the ventral visual pathway (i.e., the superior and medial temporal cortex) would be more important in the processing of visuo-spatial information in extrapersonal space. Evidence for this hypothesis has been found in transcranial magnetic stimulation (TMS) and brain imaging studies in healthy subjects [21–23]. A preliminary study regarding the anatomy of peripersonal and extrapersonal neglect in right brain-damaged patients, mainly found shared anatomical substrates based on lesion subtraction [10]. In the current study, we used continuous voxel-based lesion-symptom mapping (VLSM) in a larger sample of stroke patients to evaluate brain areas associated with neglect in peripersonal versus extrapersonal space. Contrary to lesion subtraction, continuous VLSM analysis takes into account the severity of neglect. As there is no gold standard for the threshold of neglect, and differences in used thresholds exist among studies, using a continuous outcome measures contributes to comparability between studies [24]. In order to accurately represent a stroke population, the current study included a large group of patients with left as well as right hemisphere brain damage.

Next to region of space, neglect can vary regarding frame of reference. Patients can ignore stimuli based on where they are in relation to their body (i.e., egocentric neglect) or based on whether they are part of the contralesional side of objects, irrespective of the position of the objects relative to the patient (i.e., allocentric neglect) [25]. Different neglect tests are associated with these different frames of reference. Performance on cancellation tasks is associated with egocentric representations (relative to the body of the individual), whereas performance on line bisection tasks can be associated with both egocentric and allocentric representations (object-based), dependent on the configuration of the lines [24–26,28]. We selected cancellation and bisection tasks as they are most commonly used in both clinical assessment of neglect and neglect research. Also, both are associated with the aforementioned frames of reference. Although both neglect tasks assess deficits in lateralized attention, several group studies clearly showed that double dissociations exist [e.g., 26,28]. For both tasks, dissociations have been found between peripersonal and extrapersonal neglect [11]. Furthermore, different brain areas have been associated with object finding (i.e., cancellation) versus object perception (i.e., bisection) [24,27–31]. Investigating brain areas that associate with performance on one particular task is, therefore, a more fruitful approach to unravel neural substrates compared to the use of multiple tasks, as different brain networks are likely involved in different behaviours [32].

We hypothesised that ventral areas (e.g., superior and medial temporal cortex), associated with recognition and representation of objects and scenes, would be associated with extrapersonal spatial attention [20,22]. Dorsal areas (e.g., inferior parietal cortex), which play a role in perception for action, would be associated with peripersonal spatial processing, since a person can potentially interact directly with information in peripersonal space [22]. Knowledge about the dissociation between region-specific types of neglect gains insight into the neglect syndrome, which could aid diagnosis and treatment of neglect.

2. Material and methods

2.1. Participants

Patients were retrospectively selected from a cohort of stroke patients who were consecutively admitted to De Hoogstraat Rehabilitation center in the period between October 2011 and January 2017. MRI and CT scans were obtained as standard care at admission to the hospital. Patients received a neuropsychological neglect assessment as standard care within the first two weeks after admission to the rehabilitation centre (thus, approximately four weeks after scans were made). For the current study, we included stroke patients (first or recurrent) with data of the neglect screening for both regions of space (peripersonal and extrapersonal) for at least one neuropsychological neglect task (shape cancellation or line bisection). For the lesion analyses, the following inclusion criteria were applied: (1) ischemic stroke or delayed cerebral ischemia after subarachnoid haemorrhage; and (2) delayed CT (i.e., performed >48 hours after symptom onset) or MRI brain scan available for infarct segmentation. Patients with a CT or MRI scan of insufficient quality (i.e., if the boundaries of the infarct could not reliable be delineated; e.g., due to motion artefacts) were excluded from analyses (see Figure 1 for a flowchart). The research procedures were performed in accordance with the standards of the Declaration of Helsinki.

2.2. Demographic and stroke characteristics

The following data were obtained on admission to the rehabilitation centre: age, sex, time post-stroke onset, stroke history (first, recurrent), stroke type (ischemic, subarachnoid haemorrhage), and lesion side (left, right, bilateral). Lesion volume was computed based on the CT or MRI scan. Global cognitive functioning was screened with the Mini-Mental State Examination (MMSE [33]). In addition, language communication deficits (Stichting Afasie Nederland; SAN score [34]), level of independence during daily live activities (Barthel Index [35]), and strength in both upper and lower extremities (Motricity Index [36]) were assessed.

2.3. Tasks and stimuli

In order to determine the presence of peripersonal and extrapersonal neglect, we used an experimental set-up with computerized versions of the shape cancellation (i.e., to measure egocentric neglect) and line bisection task (i.e., to measure allocentric neglect), in accordance to the one used by Van der Stoep et al. [11]. The monitor was placed at a distance of 30 cm in the peripersonal, and at 120 cm in the extrapersonal space condition. Stimuli were enlarged in the extrapersonal condition to correct for visual angle. The region of space in which the tasks were presented first, was counterbalanced between patients. The shape cancellation task was always presented first followed by the line bisection task, in the same region of space. Patients were tested in sound-attenuated dimly lit room.

2.3.1. Shape cancellation

Shape cancellation data was collected in between October 2011 and August 2014. The task consisted of 54 targets among 75 distractors. Patients had to click on targets using a computer mouse. After each click, a small circle appeared on the computer screen at the clicked location. There was no time limit. The difference in number of omissions between the left and right side of the stimulus field was computed (omission difference score). An omission difference score of ≥2 was used as an indication of neglect [11]. Based on the amount and location of missed targets, the horizontal normalized centre of cancellation (CoC-x) was computed as a measure for severity of the lateralized attention deficit [27,37]. The absolute CoC-x ranges from 0 (no neglect) up to 1 (severe neglect).

2.3.2 Line bisection

Line bisection data was collected in between October 2011 and January 2017. The task consisted of four trials with each three horizontal lines (approximately 22° long and 0.2° thick). The upper line was located in the right corner, the middle line in the middle, and the lower line in the left corner. There was a 28% vertical shift and a 15% horizontal shift with respect to the line length. Patients had to click on the subjective midpoint of each line, starting with the upper line working their way down. Per line, the average deviation was computed, resulting in a deviation score ranging from −11° to 11°. Patients with deviation scores outside the range of the performances of 28 healthy control subjects (as described in the study of Van der Stoep et al. [11]) on ≥2 lines, were labelled as 'neglect'. Subsequently, we assessed performance to categorize patients as having egocentric (i.e., marks are placed above each other) or allocentric (i.e. marks are placed at the same deviation from the midpoint of each line) neglect (Figure 2). To determine the presence of egocentric neglect, we added the value of 1.65° (which is size of the horizontal shift between lines), to the deviation of the second line and 2 * 1.65° to the deviation of the first line (see Figure 2). Then, when deviations of the first and second line, and second and third line, where within a range of 1.5° from each other, this was labelled as egocentric neglect. Patients were labelled as having allocentric neglect when deviations of the 3 lines where within a range of 1° from each other (i.e., marks were placed above each other). A third group was formed by patients with a mixed profile, these patients were excluded from further analyses.

2.4. Generation of lesion maps

The procedure for the generation of lesion maps has been previously described elsewhere [38–41]. A trained rater (JMB) who was blinded to the behavioural data manually segmented infarcts on transversal slices of either follow-up CT (n = 70), or on T2 FLAIR sequences of MRI scans (n = 64). Infarct segmentations were transformed to the Montreal Neurological Institute (MNI)-152 template [42] using the following procedure. The Elastix toolbox was used to perform all registrations [43]. An age-specific brain template was used [44], including a CT and T1 MRI template in the same coordinate space. T2 FLAIR scans were transformed to their corresponding T1 scan using a linear registration. The T1 scans were transformed to the T1 MRI template, with a linear registration followed by a non-linear registration. The registration of the CT scans to the CT template was performed using an in-house developed algorithm, which is described elsewhere [45]. The age-specific T1 MR template was transformed to the T1 MNI-152 template, with a linear and a non-linear registration. All computed transformations were composed into a single transformation step – transforming from source CT/MRI to template CT/MRI to MNI-152 – that was used to align the infarct maps directly to the MNI-152 template. The intermediate registration step using the age-specific CT/MRI template served to improve the quality of the registration by providing a better match between patient and template. The lesioned area was not masked out prior to normalisation, because the results proved to be better without masking, especially in patients with large infarcts. Quality checks of the registration results were performed by comparing the native scan to the lesion map in MNI space. For 65 patients, the co-registered lesion maps were manually adjusted to correct for slight registration errors using MRIcron (http://people.cas.sc.edu/rorden/mricron/index.html) by JMB. The voxel size after normalisation was 1x1x1 mm.

2.5. Statistical analysis

Results of the two tasks (i.e., shape cancellation and line bisection) were analysed separately. For the cancellation task, a continuous outcome measure was used for the analyses. For the line bisection task, lesion subtraction analysis was performed to be able to dissociate between egocentric and allocentric neglect.

2.5.1. Shape cancellation

Demographic and stroke characteristics: Patients were allocated to one of four groups: no neglect, peripersonal neglect, extrapersonal neglect, or neglect for both regions of space. Demographic and stroke characteristics were compared using a Kruskal-Wallis test (level of alpha = .05). In case of significant results between four groups, post-hoc Mann-Whitney analyses were performed with a Bonferroni correction for multiple testing ($p = .008$).

Lesion analyses: We used whole-brain VLSM to determine the relationship between task performance in peripersonal or extrapersonal space and the presence of a lesion in a given voxel [46]. The absolute CoC-x obtained in peripersonal and extrapersonal space conditions were introduced as continuous outcome measures. VLSM was performed using NPM and MRIcron software [47] (settings: *t*-test, univariate analysis, only including voxels that were damaged in at least five patients), before and after adjusting for total lesion volume. Correction for multiple testing was performed using a false discovery rate threshold (FDR) with $q < .05$. We additionally provided qualitative lesion overlay plots.

In addition, we performed region of interest (ROI)-based linear regression analyses, to quantify the impact of lesion volumes in specific brain areas on neglect severity. We extracted 96 cortical and 21 subcortical non-overlapping areas from the probabilistic Harvard-Oxford atlas (threshold at .25) [48]. Regions for subdivisions of gyri were merged into a single variable, thereby reducing the total number of regions to 89. In addition, we extracted regions for 16 white matter tracts from the probabilistic Johns Hopkins University White Matter Tractography Atlas (threshold at .25) [49]. All regions were projected on the VLSM results and the amount of voxels with a statistically significant correlation within each region was quantitatively assessed. Regions were considered to be associated with neglect when at least 5% of tested voxels was statistically significant associated, with a total of no less than 100 significant voxels. For each patient, the lesion volumes within these ROIs were computed and entered as independent variables in a linear regression model, with the CoC-x or average deviation score as dependent variable, after adding total lesion volume to the model.

2.5.2. Line bisection

Demographic and stroke characteristics: Per region of space, patients were allocated to one of three groups: no, allocentric or egocentric neglect. Demographic and stroke characteristics were compared using a Kruskal-Wallis test (level of alpha = .05). In case of significant results between four groups, post-hoc Mann-Whitney analyses were performed with a Bonferroni correction for multiple testing (p = .008).

Lesion analyses: In order to determine which brain regions were related to peripersonal and extrapersonal egocentric and allocentric neglect, we performed qualitative lesion overlay and subtraction analyses separately for peripersonal and extrapersonal space. In these analyses, lesion overlay and subtraction plots were generated for patients with egocentric neglect versus no neglect, and allocentric neglect versus no neglect using MRIcron.

3. Results

Of 705 patients, 134 patients were included for the VLSM analyses, of whom 98 completed the shape cancellation task and 129 the line bisection task in both regions of space (Figure 1). The most important reason for exclusion was the absence of a CT or MRI scan.

3.1. Shape cancellation

3.1.1. Demographic and stroke characteristics

Of patients who performed the shape cancellation task, 69.4% did not show neglect, 8.2% showed neglect in peripersonal space, 8.2% in extrapersonal space, and 14.3% in both regions of space. Demographic and stroke characteristics are provided in Table 1.

3.1.2. Lesion analyses

In Figure 3A the spatial distribution of the voxels that were damaged in at least five patients are depicted.

VLSM for peripersonal neglect: The results of the VLSM analyses for the CoC-x in peripersonal space are depicted in Figure 3 (panels B and C). After correction for total lesion volume, the right parahippocampal gyrus, hippocampus, thalamus, cingulum of the hippocampus, and corticospinal tract were significant associated with the CoC-x in peripersonal space (Figure 3C and Table 2).

VLSM for extrapersonal neglect: The voxels with an association between a lesion and a higher CoC-x in extrapersonal space are depicted in Figure 3 (panels D and E). Voxels within the right parahippocampal gyrus, hippocampus, thalamus, superior parietal lobule, angular gyrus, planum temporale, cingulum of the hippocampus, corticospinal tract, and to a lesser extent, supramarginal gyrus, lateral occipital cortex, superior temporal gyrus, and superior longitudinal fasciculus (temporal projections) remained significant after correction for total lesion volume (Figure 3E and Table 2). The qualitative lesion overlay plots are provided in Supplementary Figure 1.

ROI analyses for peripersonal neglect: In the linear regression model, we first added age and sex, and total lesion volume, which were not significantly associated with the CoC-x in peripersonal space (Table 3). The aforementioned regions were selected as ROIs, and their lesion volumes were included in the model. The increase in explained variance on top of age, sex and total lesion volume, was highest for lesion volume within the right parahippocampal gyrus (increase in explained variance of 26.4%; $p < .001$).

ROI analyses for extrapersonal neglect: When we inserted the CoC-x in extrapersonal space as dependent variable, age and sex were not significantly associated with extrapersonal neglect (Table 3). The total lesion volume explained an additional 6.1% ($p = .015$). The increase in explained variance on top of age, sex and total lesion volume was highest for lesion volume within the right thalamus (increase in explained variance of 20.9%; $p < .001$).

3.2. Line bisection

3.2.1. Demographic and stroke characteristics

Of patients who performed the line bisection task in peripersonal space, 7% showed allocentric and 7% showed egocentric neglect. A mixed pattern or undefined pattern was seen in 5.4% of patients, who were excluded from analyses. In extrapersonal space, 5.4% showed allocentric and 6.2% showed egocentric neglect. In 6.2% of patients a mixed or undefined pattern was seen, these patients were excluded from analyses. Individual deviations on the line bisection are depicted in Supplementary Figure 2. Demographic and stroke characteristics are provided in Table 4. It should be noted that 7 patients showed egocentric neglect in both regions of space (i.e. peripersonal and extrapersonal), whereas only 1 patient showed allocentric neglect in both regions of space. Of the 7 patients with egocentric neglect on the line bisection task, 6 performed the shape cancellation task and showed peripersonal and extrapersonal neglect on this task too.

3.2.2. Lesion analyses

Lesion overlay for peripersonal neglect: In Figure 4A-C, overlay plots of voxels that were damaged in patients without, with egocentric and allocentric peripersonal neglect are depicted. Figure 4D-E shows the subtraction plots of patients without peripersonal neglect versus patients with egocentric and allocentric peripersonal neglect respectively. Egocentric neglect was associated with right hemispheric lesions in parietal, temporal and frontal areas, including the basal ganglia. No clear pattern was observed for patients with allocentric neglect.

Lesion overlay for extrapersonal neglect: In Figure 5A-C, overlay plots of voxels that were damaged in patients without, with egocentric and allocentric extrapersonal neglect are depicted. Figure 5D-E shows the subtraction plots of patients without extrapersonal neglect versus patients with egocentric and allocentric extrapersonal neglect respectively. Right hemispheric lesions in parietal, temporal and frontal areas, including the basal ganglia, were associated with extrapersonal egocentric neglect. No clear pattern of lesions was seen in patients with allocentric neglect.

4. Discussion

Our aim was to unravel the neural substrates of peripersonal and extrapersonal neglect by applying VLSM analyses. To address this aim, analyses were performed for digitized shape cancellation (i.e., to measure egocentric neglect) and bisection tasks (i.e., to measure egocentric and allocentric neglect) separately, in two large samples of 98 and 129 stroke patients, respectively. Both patients with left- and right hemispheric damage were included to represent a general stroke population.

We evaluated the pattern of deviation on the line bisection task to dissociate between egocentric and allocentric neglect. Patients who showed egocentric neglect in peripersonal space, also showed egocentric neglect in extrapersonal space. Thus, there was no dissociation regarding region of space. There was a clear right hemispheric lateralization. Groups were too small to further specify brain areas that were involved in egocentric neglect based on the line bisection task. For allocentric neglect, there was a dissociation between patients who showed peripersonal versus extrapersonal neglect. However, in both groups, no clear lesion pattern was observed.

When neglect was measured with the shape cancellation task (i.e., egocentric frame of reference), the right parahippocampal gyrus, hippocampus, thalamus, cingulum of the hippocampus, and corticospinal tract were associated with neglect in peripersonal and extrapersonal space. The thalamus is a sensory rely station, damage to this area could affect spatial memory, which is involved in object search. The hippocampus and parahippocampus are less common associated with neglect, which could be due to the fact that we did not exclude patients with occipital lesions or visual field defects. In one study, the neural substrates of neglect (as measured with line bisection and cancellation) were separately studied in middle cerebral artery (MCA) patients and posterior cerebral artery (PCA) patients [54]. In the latter group, the parahippocampus and, to a lesser extent, the hippocampus were critically associated with neglect. There is debate regarding whether this patient group should be excluded in order to include only patients with 'pure' spatial neglect. However, an important patient group will then be missed, as patients with posterior damage often show neglect and will be underrepresented in the sample [54]. In addition, it has been shown that visual field defects from an isolated occipital lesion do not cause neglect [55], and would, therefore, not affect results.

Additionally, the right superior parietal lobule, angular gyrus, supramarginal gyrus, and planum temporale, and to a lesser extent, the right lateral occipital cortex, superior temporal gyrus, and superior longitudinal fasciculus (temporal projections) were associated with neglect in extrapersonal space only. With respect to the ventral/dorsal association hypothesis, we found that lesions in the right parahippocampal gyrus, hippocampus, and superior temporal gyrus (ventral areas), were indeed associated with neglect in extrapersonal space, however, the parahippocampal gyrus and hippocampus were *also* associated with peripersonal neglect. In addition, we found an association between lesions in dorsal areas (i.e., the supramarginal gyrus and angular gyrus) and extrapersonal neglect only. In other words, these results do not fit the ventral/dorsal hypothesis.

There is only one other study regarding lesion symptom mapping on this topic [10]. Aimola et al. [10] did report associations between specific brain areas associated with peripersonal neglect only versus extrapersonal neglect only. One explanation for the discrepancy between these studies could be the methodological differences between the study of Aimola et al. [10] and ours. First, in their study, the peripersonal and extrapersonal neglect groups consisted of only four patients, and, furthermore, no correction factors, such as lesion volume or including only voxels that are damaged in a minimum number of patients, were applied [56]. Thus, brain areas that would have been (coincidentally) damaged in only one of these patients, could immediately show up as being associated with region-specific neglect in their lesion subtraction analyses. There is, therefore, a relatively high probability of false positive findings in the study of Aimola et al. [10].

Another methodological difference is response type, which might (partly) explain differences between our study and the study of Aimola et al. [10]. In their study, patients made direct contact with the targets in peripersonal space (i.e., through the use of a pencil), whereas a laser pointer was used in extrapersonal space. This difference in response type could possibly explain different brain areas that were found to be involved with task performance. When there is sensory continuity between the patient and target, as is the case with a rod, the tool might be coded as part of the patient's hand and thus extrapersonal space may be 'remapped' into peripersonal space [57,58]. Stated differently by Neppi-Mòdona et al. [59]; "Tool use can make an object nearer or farther depending on the presence/absence of contact between the object and the agent's body". In the current study, both conditions (i.e., peripersonal versus extrapersonal) required the same type of (motor) response, with no contact between stimuli and the patient. We can therefore make neat direct comparisons between the two distances at which the stimuli were presented to the patients, yet we cannot compare differences between 'action space' and 'orientation space', as in both conditions patients could 'act' with the computer mouse in the space were the task was presented. Additionally, as there was no sensory continuity between the patient and the target in both tasks, different networks could have been involved in our peripersonal space condition compared to a paper-and-pencil cancellation task. The large overlap peripersonal and extrapersonal space conditions might explain why we mainly found overlapping brain areas, and no unique brain areas associated with peripersonal neglect. Our VLSM results therefore indicate the associated brain areas with attention processing of visual stimuli in two regions of space, but we cannot make statements on associations between regions of space, response types, and neglect (which was also not the aim of the current study). These differences in response type might, however, have serious impact on the associated brain areas. Possibly, this could explain the overlapping brain areas for egocentric peripersonal and extrapersonal neglect. However, in previous studies where only the distance was varied, keeping response type consistent, presence or severity of neglect could differ between distances [e.g., 12,15,56]. One study found no different peripersonal-extrapersonal asymmetries regarding neglect severity between perceptual (i.e. landmark task, verbal response) and motor (i.e. line bisection, manual response with laser pointer) conditions [14]. Thus, attention mechanisms could differ for different physical distances, regardless of the presence or absence of a motor component in the task.

4.1. Limitations

In the current study, we included both CT and MRI scans that were made at different post-stroke time intervals. Including both CT and MRI scans is not uncommon in lesion-symptom mapping [e.g., 31,40], as both modalities allow for accurate detection of the lesion location.

Possibly, however, the accuracy of lesion segmentation differed between modalities or scans. Nevertheless, we chose for a robust design including as many patients as possible (with either CT or MRI scans without restriction of time window) in order to optimize statistical power while accepting some heterogeneity in scan acquisition [38]. Including as many stroke patients as possible is required to study brain areas that are less frequently affected and to include sufficient patients with a cognitive deficit, given that a minority of stroke patients show signs of peripersonal or extrapersonal neglect (e.g. 25-31% in the current sample), which has a negative influence on statistical power. Furthermore, the resolution of the CT and MRI scans affects the precision of the VLSM results [38]. The in-plane voxel-size (i.e., along x- and y-axis) of the original CT and MRI scans was <1 mm, but transversal slice thickness (i.e., voxel size along the z-axis) ranged from 3 to 6.5 mm, resulting in lower precision in that direction.

It is now generally accepted that focal lesions can have devastating remote effects on the function of distant brain areas via white matter tracts [61,62]. The consequences of a lesion are determined by both lesion volume and the specific lesion location. Lesions in, for example, white matter tracts can have more severe remote consequences than cortical lesions. With respect to neglect, this disorder is assumed to be the consequence of changes in the overall frontoparietal networks rather than from a single lesioned area [61,63]. We, therefore, included ROIs for major fibre pathways in our ROI-based analyses. Unfortunately, we had no access to more advanced measures, regarding the orientation and anisotropy of white matter tracts, which can be estimated with Diffusion Tensor Imaging.

Right brain areas were predominantly associated with visuospatial neglect in this cohort, even though we included stroke patients with both left and right brain damage. Neglect following right brain damage is more frequent and severe [7–9], which might be the cause of this finding. Thus, neglect after a left-sided lesion might have been too rare in order to find a correlate with the current sample size. Alternatively, severe deficits in understanding, as part of aphasia, led to missing data. Typically, these deficits are associated with the left hemisphere. On the other hand, we have included a large, unselected sample of stroke patients compared to other lesion studies. Our sample, therefore, is more representative for a general stroke population compared to other studies.

Finally, a limitation of the current study is its retrospective nature. The choice of the neglect tasks was limited as we used that were assessed as part of usual care. Currently, the classic line bisection task (i.e. three lines of the same length on different lateral positions) is subject of debate [64,65], for example, as it appears to have low test-retest reliability [66].

Nevertheless, it is still frequently used in clinical settings. As the line bisection task might not be the most sensitive measure to detect neglect, it might explain the discrepancy between the current study and others [24,29,30]. When multiple cognitive processes could cause impaired performance during line bisection, there might be little overlap of lesions between patients with abnormal performance, resulting in non-significant findings.

4.2. Future directions and conclusions

This study identified several right temporal and thalamic areas that are associated with both peripersonal and extrapersonal egocentric neglect, and several additional right temporal, parietal and occipital areas that were specifically associated with egocentric extrapersonal neglect. Our results only partly fit the dorsal/ventral hypothesis. Most importantly, we found several overlapping brain areas for neglect in peripersonal versus extrapersonal space, suggesting that lateralized attention for different regions of space partly relies on the *same* brain network. Furthermore, several unique brain areas were associated with extrapersonal neglect when measured with a cancellation task.

Methodological differences between studies regarding neural substrates of neglect likely explain discrepant findings between studies. For example, it could relate to the response type (i.e., contact or no contact with the stimuli) that was required in peripersonal and extrapersonal space conditions. Future studies could aim to disentangle both the quality of processing visual information in different regions of space as well as pinpoint the impact of different interaction styles in different regions of space. Furthermore, variations exist with respect to inclusion criteria (mostly right-brain damaged patients without severe language deficits), sample size (small groups), time post-stroke onset, used tasks and thresholds to define neglect, scan techniques (CT versus MRI), and correction factors (e.g., lesion volume). We will discuss some of these issues and make suggestions for future research regarding neural substrates of (region-specific) visuospatial neglect.

An important issue in neglect research is the time post-stroke onset. In the current study, brain scans were made at admission to the hospital (that is, within the first days post-stroke onset), whereas the neglect tasks were administered around 1 month post-stroke onset. In the first three months post-stroke onset, most of the spontaneous neurobiological recovery takes place [67]. Immediately after stroke, for example, the blood supply to several brain areas can be distorted, leading to temporary dysfunction of the visuospatial attention system. Brain areas that are associated with visuospatial attention processes, however, could still be structurally intact. Measuring neglect immediately after stroke, and relate this behaviour to lesion locations would, therefore, not enhance insight, as patients *without* lesions in relevant areas could also show neglect, due to the aforementioned temporary dysfunction. In this case, brain areas that are not associated with lateralized attention will emerge from the VLSM analysis. It is, therefore, more informative to assess behaviour when these temporary dysfunctions are resolved (e.g. when the blood supply is restored). In a later phase, however, reorganization of cognitive functions could have taken place in the brain. Thus, some of the patients with damage in areas that are normally associated with neglect, could show *no* neglect due to this reorganization. In this case, brain areas that are critical for lateralized attention will not emerge from the VLSM analysis. We believed that after four weeks most temporary dysfunction would be resolved, and no reorganization had taken place, and was therefore the most optimal moment of behavioural assessment. A solution for this issue would be the evaluation of functional networks instead of lesion locations alone. In this way, physiological changes in structural intact distant areas that are possibly associated with visuospatial attention can be revealed. Although lesion studies are a first step in order to gain insight into the potentially affected (key) brain areas associated with neglect subtypes, insights into the remote effects of such lesions are crucial in order to fully understand attentional processes. In the future, focus should, therefore, be on (the recovery of) functional brain networks [63].

Furthermore, improved performances over time could be due to a lack of *sensitivity* of the tasks that were used and/or learning or strategic effects [19,68]. Paper-and-pencil tasks are largely 'static', there is little interference of distractors, and patients can focus on one goal. In such tasks, some neglect patients could apply compensatory strategies, mimicking 'normal' performances, while neglect is still present in daily activities. Dynamic multitasks for neglect are more sensitive and less affected by compensatory strategies. Using such tasks, therefore, could improve detection of neglect patients. In addition, studies regarding the neural substrates of neglect should focus on *specific* neglect tasks (i.e., no test batteries or combined scores), in order to be able to draw conclusions regarding specific types of behaviour. Examples are computerized tasks, with a component of timing (e.g., Temporal Order Judgement [69]) or dual-tasking [70,71]. Such tasks could be administered in two regions of space, in order to measure peripersonal versus extrapersonal neglect. Furthermore, the *severity* of neglect should be taken into account (i.e., use a continuous measure). In this case, no (arbitrary) threshold has to be used, which enhances comparability between studies.

Finally, in most neglect studies, only patients with right hemispherical damage have been included. Neglect could, however, also occur following left hemispherical damage [7–9]. As differences exist regarding frequency, severity, and region-specify in left- versus right-sided neglect [9], possibly, neural substrates are not comparable, and should be evaluated separately. In order to do so, large samples of unselected stroke patients should be included.

To conclude, no unique brain areas were associated with peripersonal neglect, neither in egocentric nor in allocentric frames of reference. We could therefore not conclusively verify the ventral/dorsal hypothesis. This study did show that several brain areas were specifically associated with extrapersonal neglect, but only in the egocentric reference frame, confirming the different attention mechanisms involved in these frames of reference.

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Table 1. Demographic and stroke characteristics, median (interquartile range) or percentage split per group. Groups are based on the **shape cancellation task** (N = 98[1]).

Outcome	No neglect		Peripersonal neglect		Extrapersonal neglect		Neglect for both regions of space		Statistics	Significant post-hoc comparisons
	N	*Mdn (IQR)*	*N*	*Mdn (IQR)*	*N*	*Mdn (IQR)*	*N*	*Mdn (IQR)*		
Age (years)	68	58 (20)	8	61 (16.)	8	57 (13)	14	50 (25)	$\chi^2(3) = 3.51$, $p = .320$	
Sex, % male	68	66.2%	8	50.0%	8	75.0%	14	57.1%	$\chi^2(3) = 1.53$, $p = .676$	
Time post-stroke (days)	68	22 (10)	8	33 (27)	8	40 (31)	14	32 (73)	$\chi^2(3) = 17.07$, $p = .001$	N-E, N-B
Stroke history, % first	61	91.8%	8	87.5%	8	87.5%	14	100%	$\chi^2(3) = 1.71$, $p = .635$	
Stroke type, % ischemic	68	94.1%	8	100%	8	100%	14	85.7%		
Lesion side	68		8		8		14		$\chi^2(3) = 2.67$, $p = .445$	
% Left		41.2%		50.0%		50.0%		7.1%		
% Right		47.1%		37.5%		50.0%		85.7%		
% Both		11.8%		12.5%		0%		7.1%		
Lesion volume (ml)	68	26 (73)	8	20 (81)	8	171 (140)	14	164 (228)	$\chi^2(3) = 21.10$, $p < .001$	N-E, N-B, P-B
MMSE (0-30)	45	27 (5)	6	26 (5)	5	27 (4)	10	28 (2)	$\chi^2(3) = 3.21$, $p = .360$	
SAN (1-7)	57	6 (2)	8	7 (1)	7	6 (6)	11	6 (1)	$\chi^2(3) = 4.43$, $p = .219$	
Barthel Index (0-20)	55	15 (9)	7	13 (9)	7	12 (10)	11	8 (4)	$\chi^2(3) = 6.48$, $p = .091$	
Motricity Index arm (0-100)	55	76 (61)	8	84 (24)	6	36 (79)	11	39 (84)	$\chi^2(3) = 6.33$, $p = .097$	
Motricity Index leg (0-100)	54	91 (27)	8	84 (28)	6	70 (87)	11	58 (83)	$\chi^2(3) = 7.88$, $p = .049$	
Shape cancellation, CoC-x (0-1)	68		8		8		14			
Peripersonal space		.000 (.003)		.036 (.045)		.001 (.009)		.074 (.081)	$\chi^2(3) = 57.19$, $p < .001$	N-P, N-B, P-E, E-B
Extrapersonal space		.000 (.000)		.002 (.015)		.020 (.013)		.063 (.169)	$\chi^2(3) = 62.94$, $p < .001$	N-F, N-B, P-B, E-B

Abbreviations: B, neglect for both regions of space; E, extrapersonal neglect; N, no neglect; MMSE, Mini-Mental State Examination; P, peripersonal neglect; SAN, Stichting Afasie Nederland.

[1]Group sizes differ per variable due to missing data.

Table 2. Voxel-based lesion-symptom mapping results for the **shape cancellation task**: tested and significant voxels for each region after correction for total lesion volume.

Anatomical regions	Patients with lesion (n)[a]	Region size in voxels (n)	Tested voxels (n)	Significant voxels in peripersonal space (n [%])	Significant voxels in extrapersonal space (n [%])
Grey matter					
R parahippocampal gyrus	15	7870	418	377 (90.19%)	377 (90.19%)
R hippocampus	15	5748	1369	1179 (86.12%)	1106 (80.79%)
R thalamus	29	10238	1891	1030 (54.47%)	1081 (57.22%)
R superior parietal lobule	21	11800	7851	0	2471 (31.47%)
R angular gyrus	20	11704	11588	0	3342 (28.84%)
R planum temporale	27	3538	3538	0	756 (21.37%)
R supramarginal gyrus	30	16304	16292	0	1778 (10.91%)
R lateral occipital cortex	23	54872	14700	0	1345 (9.15%)
R superior temporal gyrus	25	5509	5483	0	344 (6.27%)
White matter					
R cingulum of the hippocampus	5	798	195	195 (100%)	195 (100%)
R corticospinal tract	37	5021	3112	206 (6.62%)	483 (15.52%)
R superior longitudinal fasciculus (temporal projections)	31	1956	1929	0	133 (6.89%)

Abbreviation: R, right. Regions for which our criterion for involvement was met (i.e. ≥5% of tested voxels had a statistically significant association between the presence of a lesion and the CoC-x, with a minimum of 100 significant voxels) are shown here; the remaining regions are not shown.

[a] Indicates how many of the 98 patients had a lesion (≥1 voxel) within the specified region.

Table 3. Results of linear regression models with CoC-x (**shape cancellation task**) in peripersonal and extrapersonal space as outcome after correction for total lesion volume.

		Peripersonal space			***Extrapersonal space***		
Model	**Independent variables**	R^2	$p\Delta R^2$	***B* (95% CI)**	R^2	$p\Delta R^2$	***B* (95% CI)**
1	Age, sex	.008	.685		.003	.864	
2	Model 1 + total lesion volume	.014	.454	.00 (.00 to .00)	.064	.015*	.00 (.00 to .00)
3a	Model 2 + R parahippocampal gyrus	.278	<.001*	.10 (.07 to .13)	.202	<.001*	.05 (.03 to .07)
3b	Model 2 + R hippocampus	.102	.003*	.05 (.02 to .08)	.110	.031*	.02 (.00 to .04)
3c	Model 2 + R thalamus	.242	<.001*	.06 (.04 to .09)	.273	<.001*	.04 (.02 to .05)
3d	Model 2 + R superior parietal lobule	-			.184	<.001*	.01 (.01 to .02)
3e	Model 2 + R angular gyrus	-			.213	<.001*	.01 (.01 to .02)
3f	Model 2 + R planum temporale	-			.169	.001*	.02 (.01 to .04)
3g	Model 2 + R supramarginal gyrus	-			.142	.005*	.01 (.00 to .01)
3h	Model 2 + R lateral occipital cortex	-			.080	.216	.00 (-.00 to .00)
3i	Model 2 + R superior temporal gyrus	-			.066	.649	.00 (-.01 to .01)
3j	Model 2 + R cingulum of the hippocampus	.242	<.001*	.34 (.21 to .47)	.187	<.001*	.16 (.07 to .24)
3k	Model 2 + R corticospinal tract	.028	.247	.02 (-.01 to .05)	.102	.051	.02 (.00 to .04)
3l	Model 2 + R superior longitudinal fasciculus (temporal projections)	-			.106	.041*	.03 (.00 to .06)

Abbreviation: R, right. The explained variance (R^2) of CoC-x on the shape cancellation is given for each model with the corresponding *p*-value for the difference in explained variance (ΔR^2) between the model and the previous model. The unstandardized coefficient (B) applies to the change in CoC-x for every 1 ml increase in lesion volume with higher CoC-x meaning more severe neglect.

*Statistically significant with an alpha-level of $p<.05$.

Table 4. Demographic and stroke characteristics, median (interquartile range) or percentage split per group. Groups are based on the **line bisection task in peripersonal space** ($N = 122$[1]).

	No neglect		Egocentric neglect		Allocentric neglect			Significant post-hoc
Outcome	*N*	*Mdn*	*N*	*Mdn*	*N*	*Mdn*	Statistics	comparisons
Age (years)	104	56 (21)	9	61 (25)	9	62 (22)	$\chi^2(2) = 0.78$, $p = .677$	
Sex, % male	104	60.6%	9	100%	9	44.4%	$\chi^2(2) = 6.80$, $p = .033$	
Time post-stroke (days)	104	23 (15)	9	44 (104)	9	21 (10)	$\chi^2(2) = 11.01$, $p = .004$	no-ego, ego-allo
Stroke history, % first	94	87.2%	8	100%	7	85.7%	$\chi^2(2) = 1.18$, $p = .553$	
Stroke type, % ischemic	104	94.2%	9	100%	9	100%	$\chi^2(2) = 1.09$, $p = .579$	
Lesion side	104		9		9		$\chi^2(4) = 8.10$, $p = .088$	
% Left		35.6%		11.1%		44.4%		
% Right		46.2%		88.9%		55.6%		
% Both		18.3%		0%		0%		
Lesion volume (ml)	104	26 (97)	9	274 (327)	9	25 (67)	$\chi^2(2) = 10.95$, $p = .004$	no-ego
MMSE (0-30)	73	28 (4)	6	27 (3)	6	28 (7)	$\chi^2(2) = 0.13$, $p = .938$	
SAN (1-7)	88	6 (2)	8	5 (2)	8	7 (3)	$\chi^2(2) = 3.22$, $p = .200$	
Barthel Index (0-20)	85	14 (9)	8	8 (5)	8	15 (11)	$\chi^2(2) = 4.88$, $p = .087$	
Motricity Index arm (0-100)	85	76 (64)	8	9 (71)	8	77 (24)	$\chi^2(2) = 5.84$, $p = .054$	
Motricity Index leg (0-100)	84	91 (36)	8	38 (87)	8	92 (25)	$\chi^2(2) = 5.18$, $p = .075$	
Line bisection in peripersonal space, deviation in degrees	104	0.32 (0.29)	9	1.45 (1.53)	9	0.93 (0.36)	$\chi^2(2) = 44.27$, $p < .001$	no-ego, no-allo, ego-allo

Abbreviations: MMSE, Mini-Mental State Examination; SAN, Stichting Afasie Nederland.

[1] Group sizes differ per variable due to missing data.

Table 5. Demographic and stroke characteristics, median (interquartile range) or percentage split per group. Groups are based on the **line bisection task in extrapersonal space** ($N = 121$[1]).

	No neglect		Egocentric neglect		Allocentric neglect			Significant post-hoc
Outcome	*N*	*Mdn*	*N*	*Mdn*	*N*	*Mdn*	Statistics	comparisons
Age (years)	106	56 (20)	8	50 (28)	7	63 (19)	$\chi^2(2) = 1.77$, $p = .412$	
Sex, % male	106	63.2%	8	100%	7	57.1%	$\chi^2(2) = 4.66$, $p = .097$	
Time post-stroke (days)	106	23 (15)	8	60 (86)	7	18 (6)	$\chi^2(2) = 13.10$, $p = .001$	no-ego, ego-allo
Stroke history, % first	96	86.5%	7	100%	4	100%	$\chi^2(2) = 1.70$, $p = .428$	
Stroke type, % ischemic	106	95.3%	8	100%	7	85.7%	$\chi^2(2) = 1.72$, $p = .423$	
Lesion side	106		8		7		$\chi^2(4) = 8.87$, $p = .002$	
% Left		35.8%		0%		42.9%		
% Right		46.2%		100%		42.9%		
% Both		17.9%		0%		14.3%		
Lesion volume (ml)	106	26 (99)	8	308 (304)	7	22 (90)	$\chi^2(2) = 14.50$, $p = .001$	no-ego, ego-allo
MMSE (0-30)	75	28 (3)	6	28 (3)	3	25 (-)	$\chi^2(2) = 2.20$, $p = .333$	
SAN (1-7)	92	6 (2)	6	6 (1)	4	6 (1)	$\chi^2(2) = 0.82$, $p = .665$	
Barthel Index (0-20)	87	14 (9)	6	9 (5)	4	12 (7)	$\chi^2(2) = 2.36$, $p = .308$	
Motricity Index arm (0-100)	89	76 (75)	6	9 (79)	4	88 (23)	$\chi^2(2) = 3.88$, $p = .144$	
Motricity Index leg (0-100)	88	83 (36)	6	38 (81)	4	83 (23)	$\chi^2(2) = 3.56$, $p = .169$	
Line bisection in extrapersonal space, deviation in degrees	106	0.39 (0.30)	8	1.70 (1.51)	7	1.26 (0.54)	$\chi^2(2) = 23.47$, $p < .001$	no-ego, no-allo, ego-allo

Abbreviations: MMSE, Mini-Mental State Examination; SAN, Stichting Afasie Nederland.

[1] Group sizes differ per variable due to missing data.

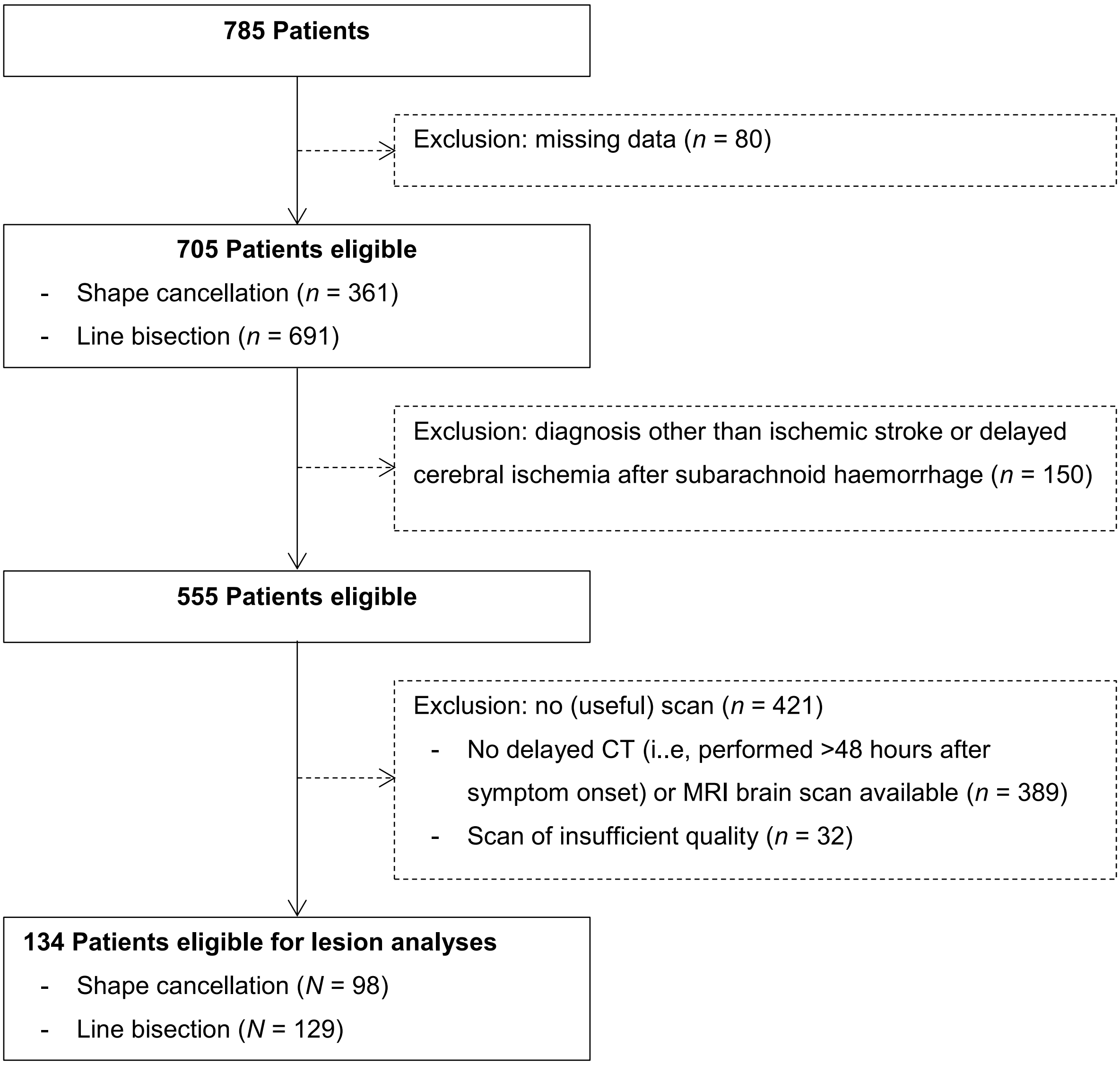

Figure 1. Flowchart of patient inclusion

Figure 2. Examples of egocentric (left pane) and allocentric (right pane) neglect.

Figure 3. Distribution of ischemic lesions and VLSM results for the shape cancellation task ($N = 98$). The results are projected on the MNI-152 template (z coordinates:−30, −15, 0, 15, 30, 45, 60). The right hemisphere is depicted on the right. (A) Voxels that are damaged in at least five patients are plotted. The coloured bar indicates the number of patients with a lesion for a given voxel. Map of the voxel wise association (t-statistic) between the presence of a lesion and the absolute CoC-x value (B) in peripersonal space, (C) in peripersonal space adjusted for total lesion volume, (D) in extrapersonal space, (E) in extrapersonal space adjusted for total lesion volume. Voxels exceeding the FDR threshold ($q = .05$) are rendered on a scale from red to yellow.

Figure 4. Lesion overlay plots and subtraction plots for patient groups based on the line bisection task in peripersonal space . The results are projected on the MNI-152 template (z coordinates:−30, −15, 0, 15, 30, 45, 60). The right hemisphere is depicted on the right. Damaged voxels are depicted for patients with (a) no peripersonal neglect ($N = 104$), (b) egocentric peripersonal neglect ($N = 9$), and (c) allocentric peripersonal neglect ($N = 9$). The colored bar indicates the number of patients with a lesion for each voxel. The final two panels show subtraction plots of patients without peripersonal neglect versus patients with (d) egocentric peripersonal neglect, and (e) allocentric peripersonal neglect. Voxels in the lesion subtraction plot that are more often damaged in the neglect group than in the no neglect group are shown on a scale ranging from pink (1% absolute difference in lesion frequency) to red (>60% absolute difference).

Figure 5. Lesion overlay plots and subtraction plots for patient groups based on the line bisection task in extrapersonal space . The results are projected on the MNI-152 template (z coordinates:−30, −15, 0, 15, 30, 45, 60). The right hemisphere is depicted on the right. Damaged voxels are depicted for patients with (a) no extrapersonal neglect ($N = 106$), (b) egocentric extrapersonal neglect ($N = 8$), and (c) allocentric extrapersonal neglect ($N = 7$). The colored bar indicates the number of patients with a lesion for each voxel. The final two panels show subtraction plots of patients without extrapersonal neglect versus patients with (d) egocentric extrapersonal neglect, and (e) allocentric extrapersonal neglect. Voxels in the lesion subtraction plot that are more often damaged in the neglect group than in the no neglect group are shown on a scale ranging from pink (1% absolute difference in lesion frequency) to red (>60% absolute difference).

Supplementary material

Supplementary Figure 1. Lesion overlay plots, groups based on performance at the shape cancellation task (*N* = 98). The results are projected on the MNI-152 template. The right hemisphere is depicted on the right. The overlay plots show the number of patients with a lesion for a given voxel separately for patients (A) without neglect (*n* = 68), (B) any type of neglect (*n* = 30), (C) peripersonal neglect (*n* = 8), (D) extrapersonal neglect (*n* = 8), (E) and neglect in both regions of space (*n* = 14).

Supplementary Figure 2. Deviations on the line bisection in peripersonal (left pane) and extrapersonal space (right pane) for individual patients with neglect. Deviations from the middle the line are depicted for each of the lines.